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EXTENSIVE HEPATECTOMY IN TWO STAGES : AN EXPERIMENTAL STUDY

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EXTENSIVE HEPATECTOMY IN TWO STAGES AN EXPERIMENTAL STUDY

by

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INTRODUCTION

Hepatic surgery has made great advances in recent years. The excellent studies on the intrahepatic vascular architecture and segmental division of the liver by HJORTSJÖ (1951)¹⁾ and HEALEY (1954)²⁾ have established a sound anatomical basis for resection of the liver with satisfactory hemostasis and preservation of adequate venous and arterial blood flow and biliary drainage. Accordingly total right hepatic lobectomy has become possible ; the reports of its successful trial have been contributed in succession by HONJO (1950)³⁻⁴⁾, WANGENSTEEN (1951)⁵⁾, LORTAT-JACOB (1952)⁶⁾, QUATTLEBAUM (1953)⁷⁾ and PACK (1953, 1955)⁸⁻⁹⁾.

Despite an increasing desirability of excisional therapy for a number of hepatic diseases, the extensive hepatectomy has been a comparatively rare surgical procedure for the fear of subsequent hepatic failure after massive resection. THOREK¹⁰⁾ stated that massive hepatectomy can be done only when it has been established that the remaining liver is fully capable of functioning alone.

There are not a few cases in which the remaining liver fails to compensate the function of the resected hepatic tissue and the resection leads into fatal hepatic insufficiency when functionally affected liver is extensively removed. Particularly in the cases complicated with cirrhosis, there is a great risk of death in early postoperative stage, as they have been accompanied with hepatic dysfunction as well as circulatory disturbance. Accordingly it is considered that the extensive hepatectomy can not be done in such cases.

In addition, THOREK pointed out that the chief error in such surgery would be failure to ascertain the precise condition and functional capacity of the unoperated side. There is, however, no method to enable us to ascertain the functional condition of the liver at the present medical situation. It has often been experienced that the operation results in failure on account of latent existence of intrahepatic cholangitis and other lesions although no abnormalities have been demonstrated in the liver function tests.

The author set about the present study in an attempt to establish the method which permits us a safe performance of extensive resection of such a diseased liver.

In planning the extensive hepatectomy for a damaged liver, it seems necessary to enhance the decreased functional capacity of the liver to prevent the postoperative hepatic insufficiency.

RAUS and LARIMORE¹¹⁾ have shown that the occlusion of portal branches to a part of the liver leads to a progressive atrophy of the parenchyma in the region deprived of portal blood, and to hypertrophy of the rest of the hepatic tissue which receives such blood in excess.

A method of the liver resection performed in two stages was devised, applying the above-mentioned phenomenon to an extensive resection of the diseased liver; the portal branches to the hepatic segments destined to be resected are ligated in the first operation, and then the resection of the segments is performed after the lapse of a certain period, during which the remaining unligated region of the liver hypertrophies with an increase of its reserve capacity. Accordingly it can be expected to mitigate the postoperative liver failure. In addition, the operation itself would become facile because the resected segments have diminished in volume.

It is considered that the extensive hepatectomy based on this idea can be utilized in practice if occlusion of the portal blood flow to the major segment of the liver can be done without producing significant physiologic disturbances.

This study was undertaken to evaluate the effects of the segmental occlusion of the portal branches upon the liver function, portal and systemic circulation in an effort to investigate the possibility of the extensive resection for the damaged liver employing this new method.

MATERIALS

The present experiments were made on normal rabbits and on the rabbits in which cirrhosis and intrahepatic cholangitis were provoked respectively in order to use them as an example of the diseased liver in clinical case.

Cirrhosis was produced in rabbits by subcutaneous injection of 0.1ml of carbon tetrachloride per kg body weight, twice a week for 4 months.

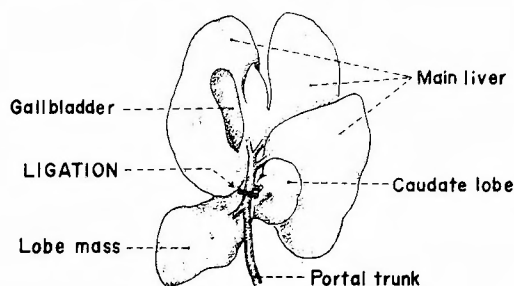
For the production of cholangitis, the emulsion of the dog gallbladder was added with an equal volume of adjuvant (mixture of 1.5 vol. arcel A oil and 8.5 vol. paraffin oil containing dead tubercle bacillus in the ratio of 1 mg per ml) and homogenized. Two ml of the resulting emulsion was intramuscularly injected to induce allergic cholangitis. Further 3 weeks later, approximately 10^{10} of *E. coli* which had been collected from the rectum of the rabbit were injected into the mesenteric vein for the production of infectious cholangitis¹²⁾.

METHODS

The rabbit liver is lobulated as illustrated in Fig. 1, of which the main liver and caudate lobe were subjected to the resection in the present investigation. In 10 normal rabbits, weight of the liver occupies 3.28% of the body weight on an average. The main liver formed 75.6% of total liver weight, the caudate lobe 4.8% and lobe mass 19.6%. The weight of the region to be resected reached to approximately 80% of the total liver (Tab. 1).

This percentage was nearly maintained in both the cirrhotic and the cholangitic rabbits.

Fig. 1 Anatomy of rabbit's liver
(Caudal aspect)



Tab. 1 Lobe mass's proportion of total liver weight and liver's proportion of body weight in normal rabbits.

Rabbit No.	Sex	Body weight (kg)	Total liver weight (g)	Lobe mass		Liver's per cent of body weight
				Weight (g)	Per cent of total liver	
1	M.	1.95	65.3	12.8	19.6	3.35
2	M.	2.10	67.1	13.9	22.2	3.19
3	M.	1.90	55.4	11.7	21.1	2.92
4	M.	2.15	73.8	12.4	16.8	3.43
5	M.	2.05	64.8	14.1	21.8	3.64
6	F.	1.80	56.4	11.0	19.5	3.19
7	F.	2.25	81.2	13.5	16.7	3.61
8	F.	2.05	64.5	13.3	20.6	3.15
9	F.	1.70	55.0	8.9	16.2	3.24
10	F.	2.15	66.2	14.2	21.5	3.08
Average					19.6%	3.28%
Resected lobe's mean proportion of total liver weight					80.4%	

I. Operative procedure

Normal, cirrhotic and cholangitic rabbits were divided into two series respectively and following operations were given with sterile technique under ether anesthesia.

(1) Eighty per cent hepatectomized group in two-stage operation

(a) First operation

The running of the extrahepatic portal branches is shown in Fig. 1. The portal trunk was ligated just below the caudate lobe to interrupt the portal blood flow to the main liver and caudate lobe which were destined to be resected. By such means, the whole portal stream was diverted to the lobe mass. In ligating the portal branches, great care was taken not to interfere with the hepatic artery and bile duct.

In the cases of narrow distance between the caudate lobe and the lobe mass, the caudate lobe was resected first with an intention to avoid disturbing the portal stream to the lobe mass, and then ligated the portal branches.

In the cirrhotic and the cholangitic rabbits, the caudate lobe was routinely resected for the investigation of the preoperative histological findings.

(b) Second operation

The resection of the liver was undertaken 3 weeks after the first operation in the normal and the cholangitic rabbits, and 4 weeks after the operation in the cirrhotic rabbits in taking the regenerating process of the lobe mass and postoperative transition of liver function into consideration.

The main liver and caudate lobe of which the portal branches had been ligated were isolated from the fixing ligaments and resected under mass ligature at their root.

(2) Eighty per cent hepatectomized group in one-stage operation

As a control, the main liver and the caudate lobe were resected in one stage.

Postoperatively all rabbits of each group were placed on ordinary rations as soon as they recovered from anesthesia. The administration of antibiotics and liver-protection therapy were purposely omitted.

III. Investigation items

(1) Liver changes following segmental occlusion of the portal branches

The rabbits were sacrificed at certain intervals after the ligation of the portal branches to the main liver and to the caudate lobe, and then the liver was extirpated to examine the hypertrophy process of the lobe mass and that atrophy of the lobes deprived of portal blood.

In addition, the ratio of the weight of the lobe mass to the body weight was determined to compare with the hypertrophy of the remaining lobe mass in the control group of one-stage hepatectomy.

Small pieces of the liver tissue collected at autopsy or during operation were immediately fixed in 10% neutral formalin or CARNOY's solution, and the following stainings were performed.

- (a) Hematoxylin-eosin double staining.
- (b) Glycogen staining.
- (c) Fat staining by Sudan III method.
- (d) Alkaline phosphatase staining.

(2) Liver function studies

The following tests were employed in the present investigation.

- (a) Serum proteins and albumin-globulin ratio¹³⁾.
- (b) Serum cholesterol and cholesterinester ratio¹⁴⁾.
- (c) Serum alkaline phosphatase¹⁵⁾.
- (d) Serum cholinesterase¹⁶⁾.
- (e) Serum total bilirubin¹⁷⁾.
- (f) Bromsulfalein excretion. Retention measured 10 min. after intravenous injection of Hepatosulphalein 5 mg per kg.

(3) Condition of the portal and systemic circulation

- (a) Determination of portal and arterial pressure

The portal pressure was determined by a water manometer connected to the catheter which was inserted into the portal vein from the mesenteric vein. The blood pressure was measured at the femoral artery by a mercurial manometer.

- (b) Circulating blood volume

Plasma volume was measured using Evans blue solution following the method of

GREGERSON¹⁸⁾, and the blood volume was calculated from the hematocrit value.

(c) Electrocardiography

E. C. G. tracing was performed with standard leads and unipolar limb leads.

(d) Portalography

A radiograph was taken to observe the circulatory condition in the extra- and intra-hepatic portal vein, immediately after the injection of 76% Urografin (1 ml per kg) into the mesenteric vein.

RESULTS

I. Extensive hepatectomy in the normal rabbits

(1) One-stage 80% hepatectomized group (Control group)

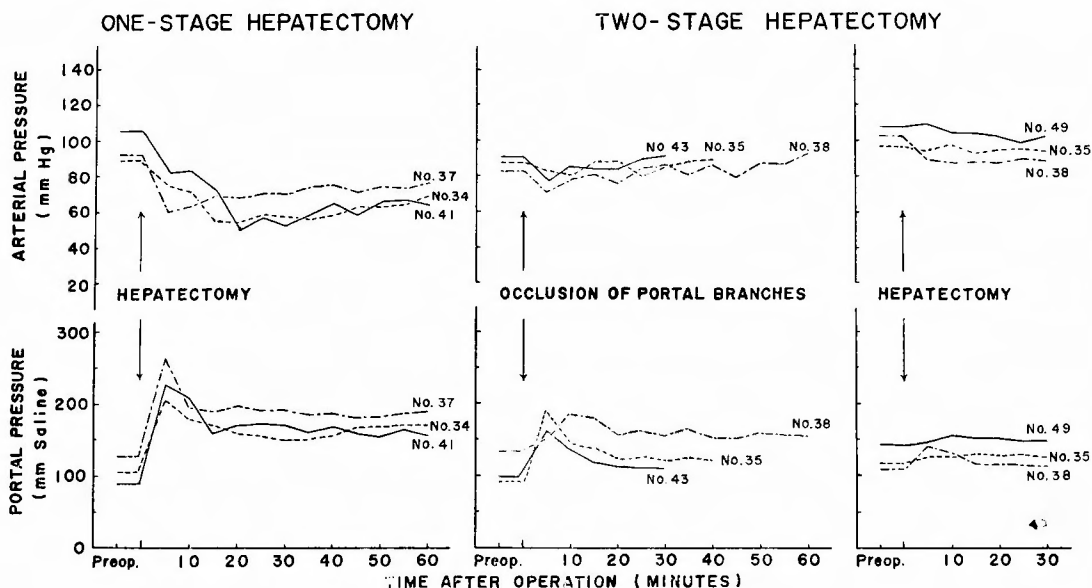
Liver changes after local ablation : Out of 12 rabbits of which the main liver and caudate lobe had been resected in one stage, only 3 cases survived long. Their remaining lobe mass weighted 3.18 to 3.41% of the body weight 6 weeks after the operation, indicating that they restored almost to the original total hepatic weight (Tab. 4).

Microscopic sections of the remaining lobe mass taken 24 hours after the operation revealed severe parenchymal damages such as congestion, hemorrhage, dissociation of cell cords and vacuolate degeneration or necrosis of liver cells. Glycogen almost disappeared, fat and alkaline phosphatase markedly increased (Fig. 4, 5, 6).

In the long survived cases, the parenchymal damages subsided gradually and proliferation of the liver cells started with an increase of glycogen and a decrease of fat. The hepatic tissue recovered its almost normal feature 4 to 5 weeks after the operation.

Portal and systemic circulation : Portal pressures showed rise of 96 to 140 mmH₂O above the preliminary pressures immediately after the one-stage 80% hepatectomy, and then gradually fell down, but they continued to show the rise of 59 to 78 mmH₂O over

Fig. 2 Changes in portal and arterial pressure (Normal rabbits)



the preoperative levels. In the portalography performed 30 minutes after the operation, circulatory disturbances such as dilatation of the extra- and intrahepatic portal vein and regurgitation of the contrast medium into the splenic vein were observed. Blood pressures abruptly dropped down and the circulating blood volume showed a decrease of 21.9 to 39.4% of the preoperative value. Three cases died, being unable to recover from the shock condition (Fig. 2, 26, Tab. 3).

Liver function studies : Abnormalities in the liver function tests were remarkable corresponding to the period of severe parenchymal damages of the remaining lobe ; brom-sulfalein retention and serum total cholesterol increased, and cholesterinester ratio and cholinesterase decreased. Decrease in serum protein and lowering of albumin-globulin ratio reached their minimum 4 to 7 days later. During that period 5 cases died. The disturbances in the liver function tests disappeared in 4 to 5 weeks in the long survived rabbits (Fig. 3).

Results of operation : Of 12 normal rabbits in which 80 % region of the liver was resected in one stage, success was obtained only in 3 cases. The remaining cases died of hepatic insufficiency or shock, with an exception of one rabbit which died of ileus on the 17th day after the operation (Tab. 4).

(2) Two-stage 80% hepatectomized group

(a) First operation

Liver changes following local portal diversion : Ligation of the portal branches to the main liver and to the caudate lobe which were destined to be resected led to the atrophy of these lobes and to hypertrophy of the unligated lobe mass. Original proportion of the lobe mass was only 19.6% of the total liver in weight on an average, it reached 37.2% one weeks later, 47.2% two weeks later, 69.6% three weeks after the first operation ; in other words, it enlarged approximately 3.5 times of its preoperative weight (Tab. 2).

Microscopic sections of the unligated lobe mass 24 hours after the operation revealed moderate congestion in the parenchyma, but there were no significant degenerative changes in the liver cells. Alkaline phosphatase amount was normal and decrease of glycogen was mild without any increase of fat. A large number of binuclear cells had already appeared in the peripheral zone of the lobules. Afterwards followed the active proliferation of the liver cells, and the lobules markedly hypertrophied 3 weeks after the operation (Fig. 7, 8, 9, 12).

On the other side, in the main liver and caudate lobe deprived of portal blood, liver cells atrophied and the parenchyma gradually decreased in amount with a relative increase in connective tissue (Fig. 13). Glycogen was demonstrated in the atrophied liver cells and bile excretion was observed from the bile ducts draining the hepatic segments which were supplied only with arterial blood.

Portal and systemic circulation : Portal pressures showed rise of 53 to 94 mmH₂O above the preliminary pressures immediately after the ligation of the portal branches to the 80% region of the liver, but they fell down comparatively fast to the levels of 12 to 26 mmH₂O over the preoperative value. There were no significant signs of the circulatory disturbances revealed out in portalogram.

Tab. 2 Hypertrophy of lobe mass after occlusion of portal branches to main liver and caudate lobe

Groups	Postoperative duration	Rabbit No.	Body weight (kg)	Total liver weight (g)	Lobe mass	
					Weight (g)	Per cent of total liver
		Normal				19.6*
Normal rabbits	1 week	22	2.15	66.7	21.6	32.1
		25	2.30	76.6	28.8	37.6
		27	2.35	74.9	31.2	41.6
	2 weeks	17	2.20	72.6	35.3	48.6
		18	1.95	62.3	24.4	39.1
		19	2.05	70.5	32.3	51.2
	3 weeks	14	2.25	79.2	59.6	75.3
		15	2.15	70.7	47.2	66.7
		16	2.30	82.4	58.7	74.9
		28	2.20	79.1	48.6	61.4
Cirrhotic rabbits	1 weeks	57	1.85	59.8	37.1	62.1
		66	1.95	63.1	37.7	59.7
		69	2.05	68.2	34.9	51.2
Cholangitic rabbits	3 weeks	72	2.15	64.3	27.1	42.1
		73	2.20	67.2	45.8	68.2
		74	2.05	59.8	26.7	41.7
		86	2.30	63.7	39.8	62.5

* Mean proportion of 10 normal rabbits

Tab. 3 Changes in circulating blood volume

Operative procedure	Groups	Rabbit No.	Preop. (cc/kg)	30 min. postop. (cc/kg)
80% hepatectomy in one stage	Normal rabbits	34	84.3	65.8 (-21.9%)
		37	98.2	59.5 (-39.4%)
		41	77.6	61.4 (-20.9%)
	Cirrhotic rabbits	62	71.5	37.1 (-48.2%)
		65	83.2	57.2 (-31.8%)
		71	69.8	41.7 (-37.2%)
Occlusion of portal branches to 80% liver area	Normal rabbits	35	82.9	75.4 (-9.1%)
		38	76.2	71.6 (-6.3%)
		43	102.7	99.8 (-2.3%)
	Cirrhotic rabbits	61	86.5	78.2 (-9.6%)
		66	72.1	58.7 (-18.8%)
		68	92.1	81.6 (-11.4%)

Blood pressures fell down slightly and they recovered in a short time. The decrease in the circulating blood volume amounted only 2.3 to 9.1 % of the preoperative value (Fig. 2, 27, Tab. 3).

Liver function studies: The disturbances in the liver function tests after the local portal diversion were generally mild. Some cases showed a decrease in serum protein with lowering of the albumin-globulin ratio and slight increase in bromsulphalein retention, but they became almost normal in 2 to 3 weeks. Serum cholinesterase and cholesterinester ratio were not significantly altered (Fig. 3).

Out of 29 rabbits whose portal branches to the 80% region of the liver had been ligated, 3 cases died. Death in the 2 animals were due to technical error. The portal vein was injured during dissection, inadequately repaired, and death resulted from secondary hemorrhage. Other one case died of ileus on the 13th day after the operation. The remaining rabbits survived until they were electively sacrificed.

(b) Second operation

The main liver and caudate lobe were resected 3 weeks after the deprivation of the portal blood supply to these lobes. The operation was technically facile because these lobes had atrophied to less than a half in volume, excluding the case which was required the separation of the adhesion between the atrophied lobes and the surrounding organs.

There were no significant variations observed in portal and arterial pressures after the second operation. Postoperative liver function tests revealed only such mild depression as seen in simple celiotomy (Fig. 2, 3).

Microscopic sections of remaining lobe mass taken 24 hours after the operation showed no congestion nor degenerative changes in liver cells. The lobe mass continued to hypertrophy becoming 2.78 to 3.67% of the body weight 3 weeks after the second operation i. e. 6 weeks after the first operation. It is indicated that the liver regeneration in this group was equal to or more active than that in the successful cases of control group hepatectomized in one stage (Fig. 14, Tab. 4).

Fig. 3 Liver function studies
(Normal rabbits)

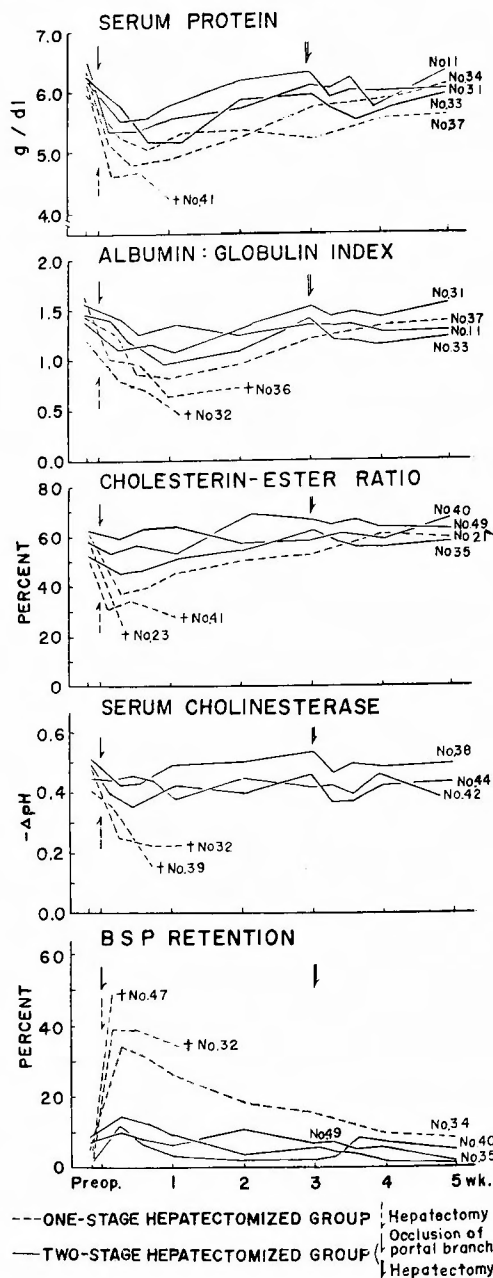


PLATE 1 NORMAL RABBITS

Lobe mass 24 hours after one-stage resection
of main liver and caudate lobe. (Rabbit 26)

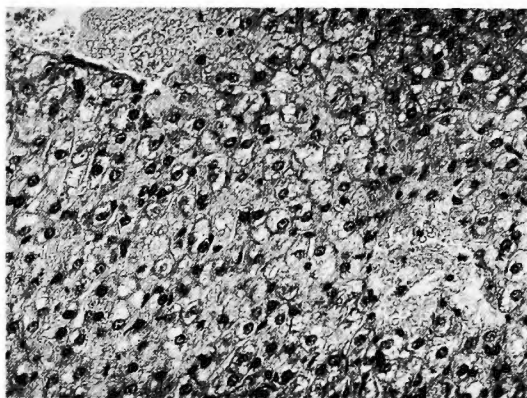


Fig. 4 H-E $\times 300$

Lobe mass 24 hours after ligation of portal
branches to main liver and caudate lobe.
(Rabbit 28)

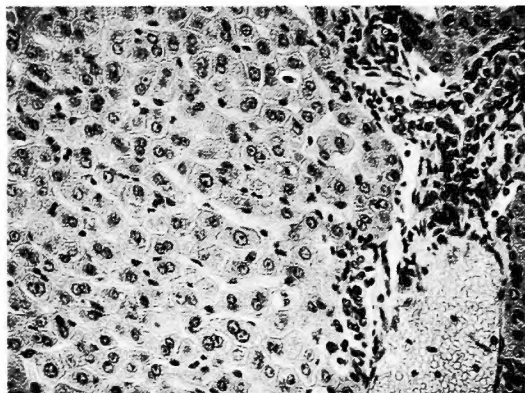


Fig. 7 H-E $\times 300$

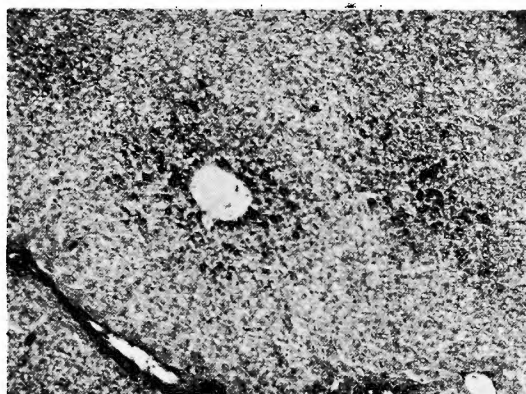


Fig. 5 Glycogen $\times 100$

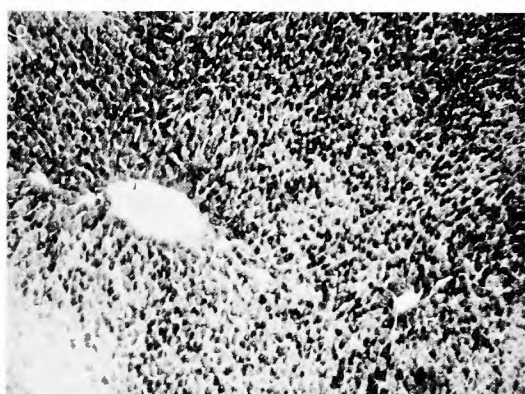


Fig. 8 Glycogen $\times 100$



Fig. 6 Alkaline phosphatase $\times 300$

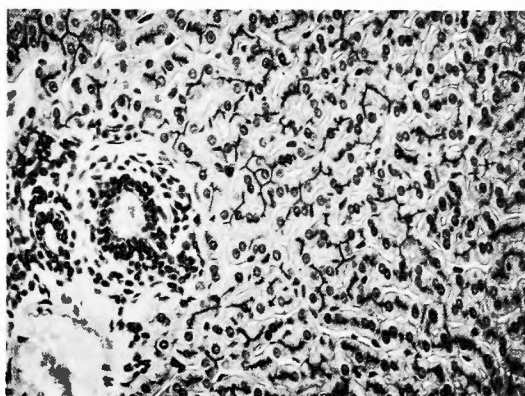


Fig. 9 Alkaline phosphatase $\times 300$

PLATE 2 NORMAL RABBITS



Fig. 10 Caudal aspect of normal rabbit's liver (Rabbit 6).



Fig. 11 Hypertrophy of lobe mass and atrophy of the main liver and caudate lobe 3 weeks after segmental occlusion of the portal blood (Rabbit 16).

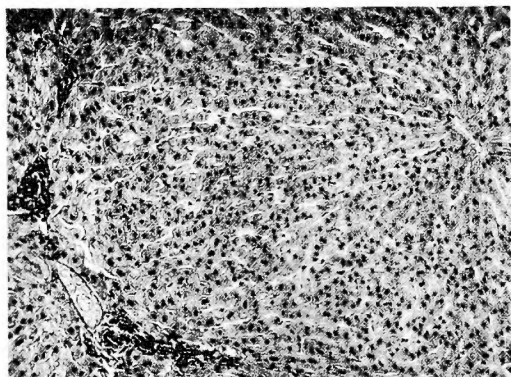


Fig. 12 Hypertrophied lobe mass 3 weeks after the ligation of the portal branch (Rabbit 16). H-E $\times 100$



Fig. 13 Atrophied main liver 3 weeks after the ligation of the portal branch (Rabbit 16). H-E $\times 100$

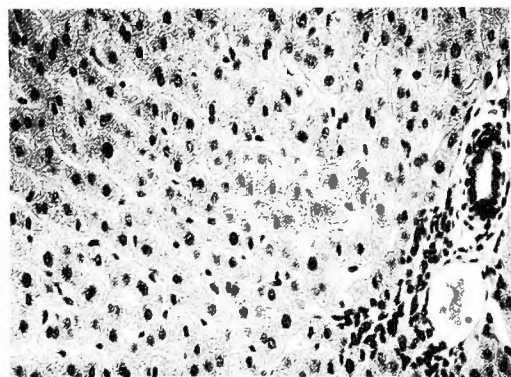


Fig. 14 Two-stage hepatectomized rabbit's remaining lobe mass 24 hours after the resection (Rabbit 46). H-E $\times 300$

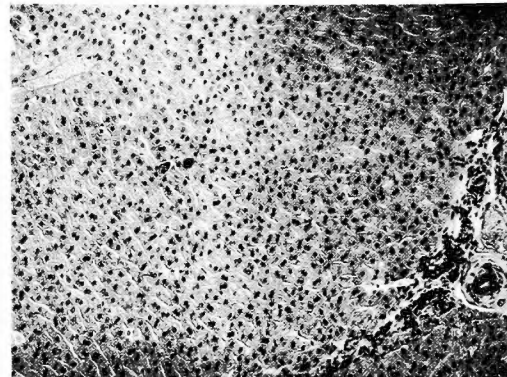


Fig. 15 Two-stage hepatectomized rabbit's remaining lobe mass 3 weeks after the resection (Rabbit 49). H-E $\times 100$

Tab. 4 Results of operation and liver regeneration (Normal rabbits)

One-stage 80% Hepatectomized Group (12 rabbits)

Rabbit No.	Length of survival	Cause of death	Liver's per cent of body weight*
20	3 hours	Shock	— — —
21	more than 6 weeks	—	3.18 (65.2g/2.05kg)
23	3 days	Liver failure	— — —
24	7 hours	Shock	— — —
32	9 days	Liver failure	— — —
34	more than 6 weeks	—	2.96 (72.5g/2.45kg)
36	17 days	Ileus	— — —
37	more than 6 weeks	—	3.41 (71.6g/2.10kg)
39	5 days	Liver failure	— — —
41	7 days	Liver failure	— — —
45	4 hours	Shock	— — —
47	3 days	Liver failure	— — —

* At autopsy 6 weeks after operation

Two-stage 80% Hepatectomized Group (12 rabbits)

Rabbit No.	Length of survival**	Cause of death	Liver's per cent of bodyweight***
11	more than 6 weeks	—	2.78 (61.2g/2.20kg)
12	3 hours	Portal injury	— — —
13	21 hours	Portal injury	— — —
31	more than 6 weeks	—	3.42 (73.5g/2.15kg)
33	more than 6 weeks	—	3.25 (71.8g/2.30kg)
35	more than 6 weeks	—	3.52 (72.2g/2.05kg)
38	more than 6 weeks	—	3.34 (63.5g/1.90kg)
40	more than 6 weeks	—	3.24 (69.7g/2.15kg)
42	more than 6 weeks	—	3.67 (61.6g/1.95kg)
43	13 days	Ileus	— — —
44	more than 6 weeks	—	3.29 (80.6g/2.45kg)
49	more than 6 weeks	—	2.91 (69.8g/2.40kg)

** Time after first operation

*** At autopsy 6 weeks after first operation

Results of operation : Out of 12 rabbits in which 80% region of the liver was resected in two stages, success was obtained in 9 cases. Three cases died of portal injury and of ileus as mentioned previously (Tab. 4).

II. Extensive hepatectomy in the cirrhotic rabbits

(1) Preoperative condition of the liver

The liver contracted as a whole and the surface was diffusely nodular and firm. The lymphatic vessels in the hepatic hilus dilated significantly and ascites appeared more or less in all the cases.

The chief histologic features were dense perilobular connective tissue, degenerative changes of liver cells, dissociation of liver cords, areas of regeneration, fatty and cellular infiltration. The grade of proliferation of the intralobular connective tissue varied case by

case, but the various findings from precirrhosis to apparent cirrhosis were observed in all the cases (Fig. 20).

In the liver function tests, increase in bromsulfalein retention, lowering of albumin-globulin ratio and cholesterinester ratio were determined, indicating moderate to severe depression of the liver function (Fig. 18).

(2) One-stage 80% hepatectomized group (Control group)

The massive resection of the cirrhotic liver exerted a great deal of influence upon the experimental animals.

Portal and systemic circulation : Portal pressures showed abrupt rise of 112 to 143 mmHg above the preliminary levels immediately after the resection of the main liver and caudate lobe, roughly showing no tendency of decline. Similarly portalography revealed not only dilatation of the portal trunk but also marked regurgitation of the contrast medium into the mesenteric veins (Fig. 16, 28).

Blood pressures fell severely and circulating blood volumes showed a decrease of 37.2 to 48.2% of the preoperative values. Also electrocardiogram revealed the depression of the S-T segment and abnormal T wave, indicating the appearance of myocardial hypoxia (Tab. 3, Fig. 17).

Three out of 4 cirrhotic rabbits which underwent one-stage 80% hepatectomy failed to recover from shock and died within 10 hours after the operation.

Liver function studies : The liver function tests could be performed in only one case that did not die in the early postoperative stage. Severe disturbances were demonstrated ; remarkable increase in bromsulfalein retention, serum bilirubin and total cholesterol, and decrease in serum protein with lowering of albumin-globulin ratio (Fig. 18). The rabbit died 5 days after the operation. Regeneration of the remaining lobe was not ascertained at autopsy.

Fig. 16 Changes in portal and arterial pressure (Cirrhotic rabbits)

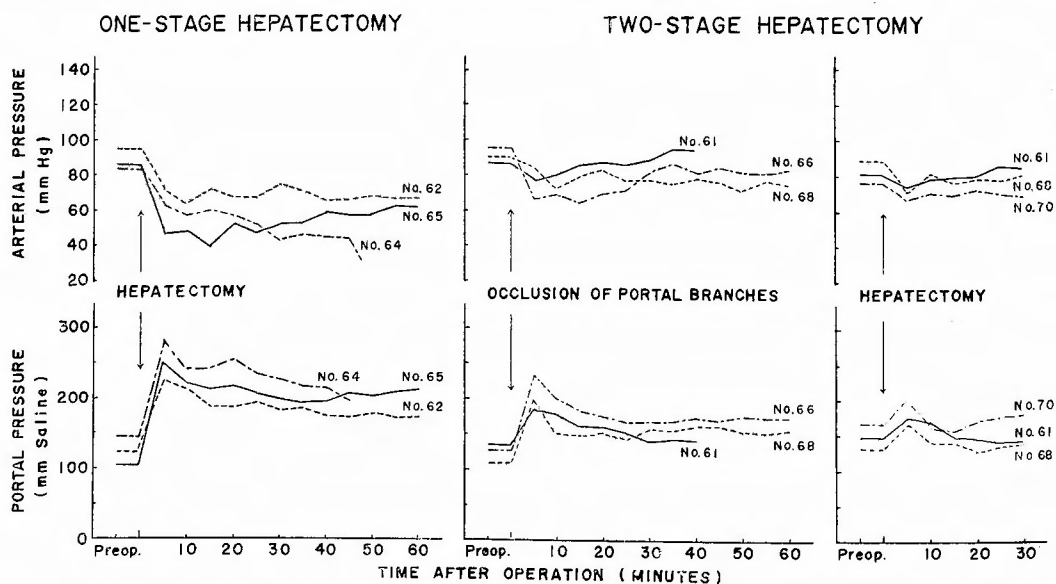
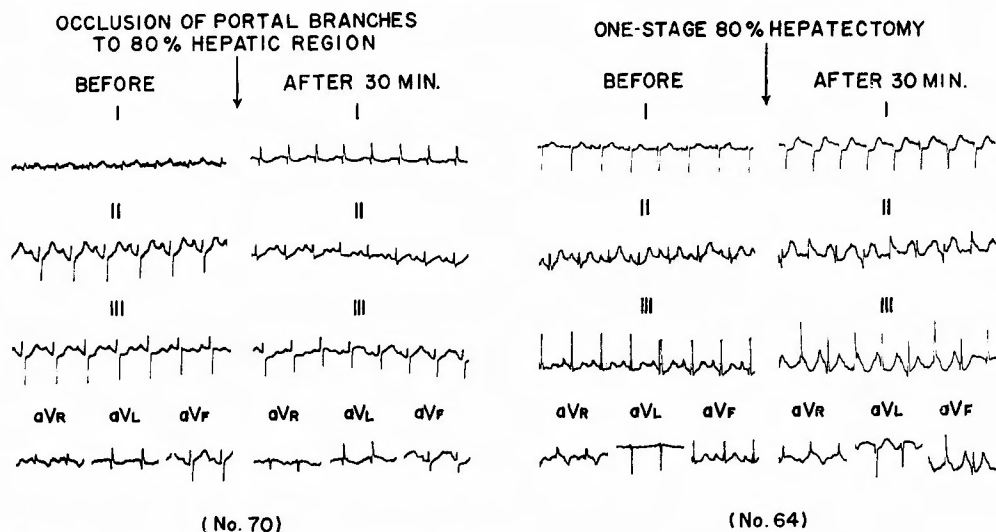


Fig. 17 Changes in electrocardiogram (Cirrhotic rabbits)



(3) Two-stage 80% hepatectomized group

(a) First operation

The possibility of occluding the portal blood supply to the major segment of the cirrhotic liver which had been accompanied with hepatic dysfunction and circulatory disturbances was examined.

Portal and systemic circulation : Immediately after the ligation of the portal branches to the main liver and caudate lobe, portal pressures showed similar rise as seen in the case of removing same segments. They fell down, however, to the levels of 18 to 43 mmH₂O above the preoperative pressures in 20 to 30 minutes. Portalogram revealed the partial dilatation of the portal trunk, but there was no regurgitation of the contrast medium (Fig. 16, 29).

Some cases showed a moderate fall of the blood pressure. Decrease in the circulating blood volume was no more than 19% of the preoperative values. In the electrocardiogram, a slight change in the S-T segment was the only sign to be observed (Tab. 3, Fig. 17).

Liver function studies : There was no postoperative aggravation which should be regarded as dangerous. In one case, serum protein decreased to 5.1% and bromsulphalein retention increased to 34%, but the depression of the function showed a tendency to recover gradually and some improvement could be observed as compared with the preoperative condition in 3 to 4 weeks after the first operation (Fig. 18).

Ligation of the portal branches to the 80% region of the cirrhotic liver was performed in 8 rabbits, there was not a single case which died of postoperative shock or hepatic insufficiency.

Melena was observed postoperatively in one case, but it subsided in 2 days, followed by favourable process. As this rabbit was employed for the determination of the portal pressure, occlusion of the mesenteric vein used for the determination is not excluded as the cause of melena.

Fig. 18 Liver function studies
(Cirrhotic rabbits)

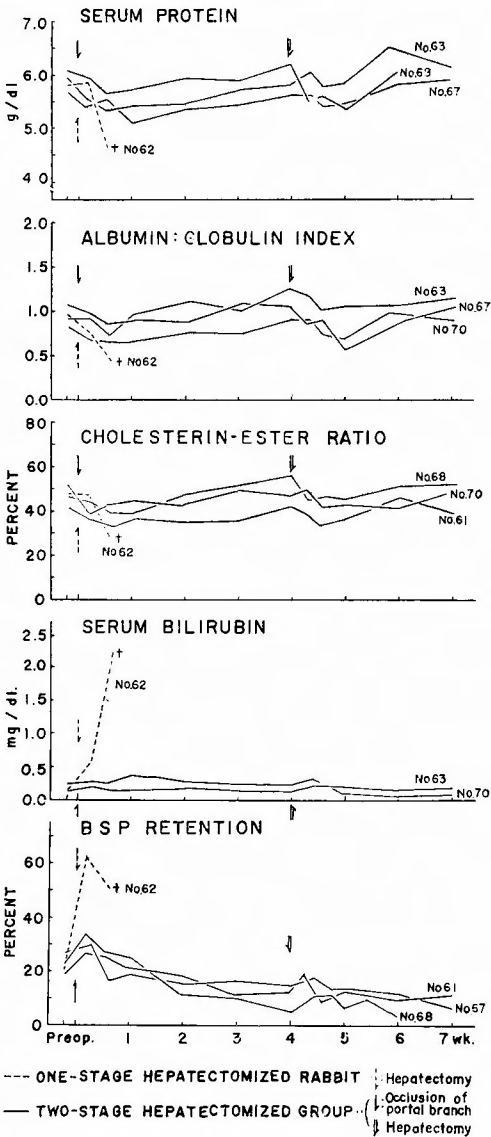
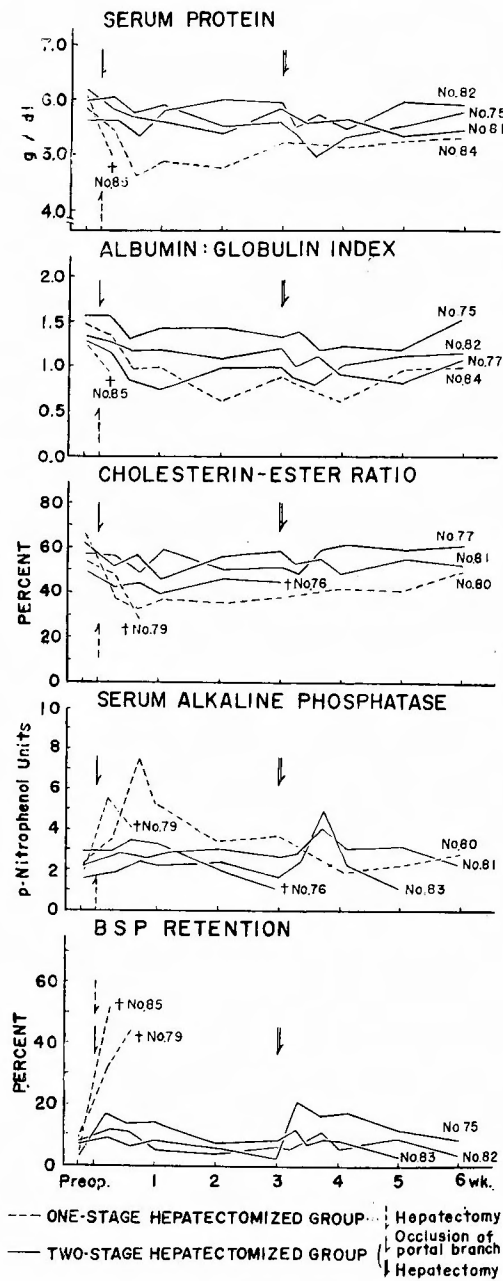


Fig. 19 Liver function studies
(Cholangitic rabbits)



Regeneration in cirrhotic liver following local portal diversion : Hypertrophy of the unligated lobe mass after the ligation of the portal branches to the main liver was more retarded than that in the normal liver. The lobe mass, however, enlarged approximately 2.9 times of the original weight in 4 weeks. The histologic findings of the hypertrophied lobe mass were more favourable than those of biopsy specimen taken at the first operation; the

PLATE 3 CIRRHOTIC RABBITS

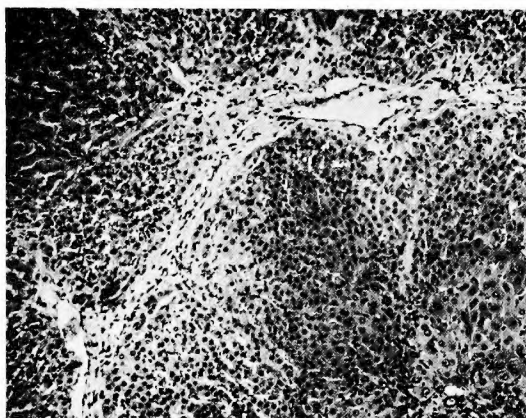


Fig. 20 Preoperative feature of the cirrhotic liver (Rabbit 66). H-E $\times 150$

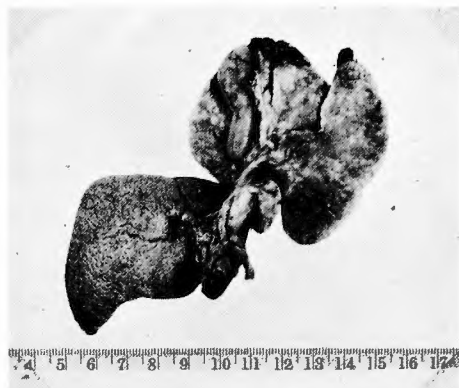


Fig. 21 Hypertrophy of the lobe mass and atrophy of the main liver and caudate lobe 4 weeks after segmental occlusion of the portal blood (Rabbit 66).

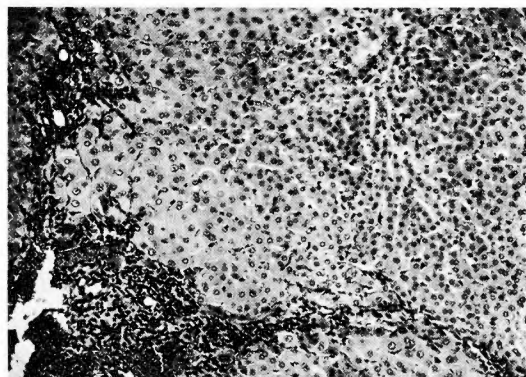


Fig. 22 Hypertrophied lobe mass 4 weeks after the ligation of the portal branch (Rabbit 66). H-E $\times 150$

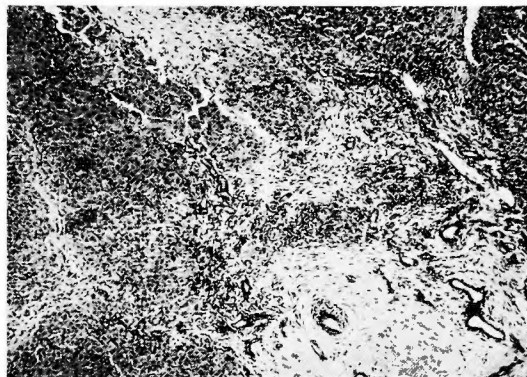


Fig. 23 Atrophied main liver 4 weeks after the ligation of the portal branch (Rabbit 66). H-E $\times 100$

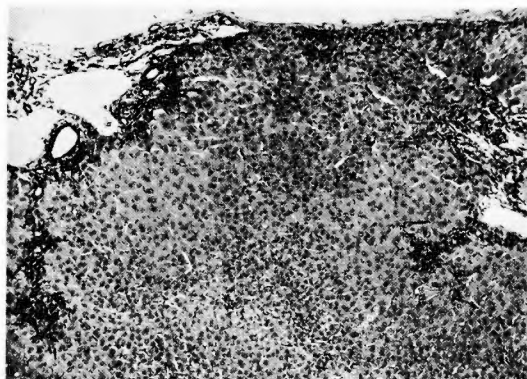


Fig. 24 Two-stage hepatectomized rabbit's remaining lobe mass 3 weeks after the resection (Rabbit 68). H-E $\times 100$



Fig. 25 Macroscopic aspect of two-stage hepatectomized cirrhotic rabbit's hypertrophied lobe mass (Rabbit 68).

PLATE 4 PORTALOGRAM

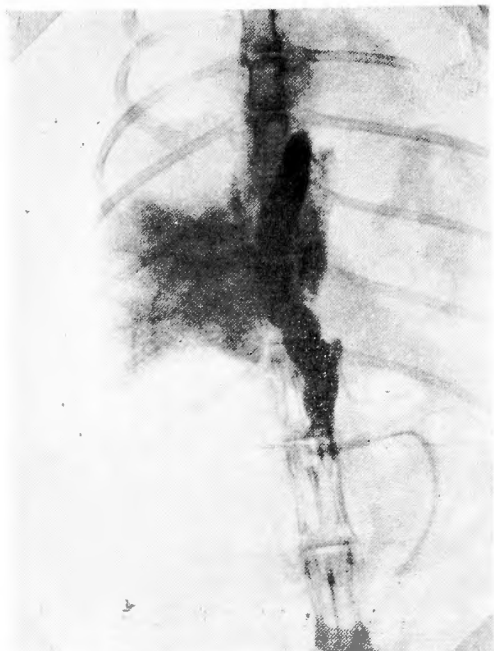


Fig. 26 30 min. after one-stage 80% hepatectomy in normal rabbit (Rabbit 36).



Fig. 27 30 min. after 80% segmental occlusion of the portal branch in normal rabbit (Rabbit 42).

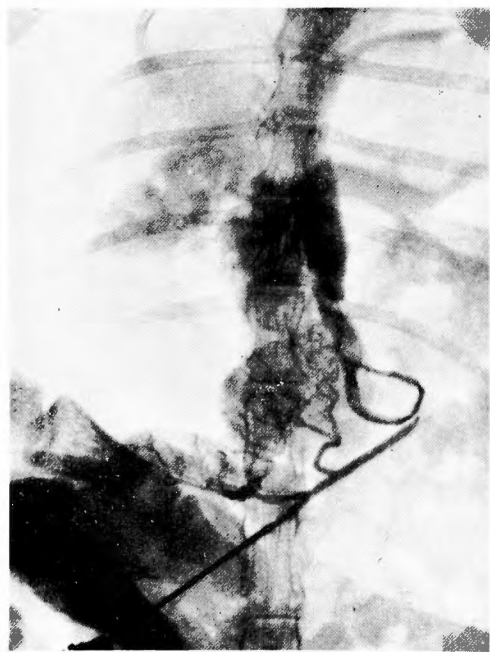


Fig. 28 30 min. after one-stage 80% hepatectomy in cirrhotic rabbit (Rabbit 71).



Fig. 29 30 min. after 80% segmental occlusion of the portal branch in cirrhotic rabbit (Rabbit 57).

Tab. 5 Results of operation and liver regeneration (Cirrhotic rabbits)

One-stage 80% Hepatectomized Group (4 rabbits)

Rabbit No.	Length of survival	Cause of death	Liver's per cent of body weight
62	5 days	Liver failure	— — —
64	55 min.	Shock	— — —
65	4 hours	Shock	— — —
71	7 hours	Shock	— — —

Two-stage 80% Hepatectomized Group (5 rabbits)

Rabbit No.	Length of survival	Cause of death	Liver's per cent of body weight*
61	more than 7 weeks	—	2.79 (58.5g/2.10kg)
63	more than 7 weeks	—	2.71 (55.6g/2.05kg)
67	more than 7 weeks	—	2.98 (64.1g/2.15kg)
68	more than 7 weeks	—	2.54 (49.6g/1.95kg)
70	more than 7 weeks	—	2.58 (54.2g/2.10kg)

* At autopsy 7 weeks after first operation

lobules enlarged with active proliferation of the liver cells and degenerative changes in the liver cells found prior to the operation were scarcely observed.

On the other side, the main liver deprived of portal blood atrophied with considerable increase in connective tissue and the parenchyma was found insulated in its distribution (Fig. 22, 23).

(b) Second operation

The atrophied main liver was resected 4 weeks after the first operation. The resulting changes in the portal and arterial pressures were comparatively mild and recovered in a short time. Postoperative liver function tests revealed a moderate decrease in serum protein, albumin-globulin ratio and in cholesterinester ratio, but they recovered almost to normal levels in 2 to 3 weeks. No significant changes were determined in the bromsul-falein test and in serum bilirubin (Fig. 16, 18).

In all 5 cirrhotic rabbits that underwent the two-stage hepatectomy, 80% region of the liver was successfully removed. The remaining lobe mass hypertrophied to the extent of 2.58 to 2.79% of the body weight 3 weeks after the resection. It regenerated as far as approximately 80% of the total liver weight of the normal rabbit.

Histologically the lobules were almost occupied by the regenerated liver cells and the perilobular connective tissue seemed to be reduced as compared with the findings of biopsy at the first operation (Tab. 5, Fig. 24, 25).

III. Extensive hepatectomy in the cholangitic rabbits

(1) Preoperative condition of the liver

The macroscopic aspects of the liver were almost normal, but microscopic sections revealed the findings of cholangitis and pericholangitis such as proliferation of the pericholangial connective tissue and epithelial hyperplasia of the bile ducts with cellular infiltration (Fig. 30).

The liver function tests revealed no abnormalities except for only a slight increase in serum alkaline phosphatase (Fig. 19).

(2) One-stage 80% hepatectomized group (Control group)

Out of 5 cholangitic rabbits whose main liver and caudate lobe had been resected in one stage, 3 cases died within one week after the operation. The remaining lobe mass was yellowish brown and friable. The microscopic sections revealed not only degenerative changes in the liver cells but also massive tissue necrosis with infection. The findings of the regeneration were not so significant (Fig. 31).

The remaining lobe mass of 2 cases which survived long showed hypertrophy amounting almost to the original total liver weight 6 weeks after the operation. Microscopically, however, focal necrosis was observed sporadically in addition to cellular infiltration (Fig. 35).

Postoperative liver function tests revealed the increase in bromsulfalein retention, in serum alkaline phosphatase and also showed the decrease in serum protein with lowering of albumin-globulin ratio and in cholesterinester ratio. Their recovery were apt to be delayed (Fig. 19).

(3) Two-stage 80% hepatectomized group

(a) First operation

In the cholangitic rabbits which underwent the ligation of the portal branches to the main liver and caudate lobe, all 10 cases survived and postoperative functional disturbances were not significant in general (Fig. 19).

Microscopic sections of the hypertrophied lobe mass 3 weeks after the ligation revealed impressive regenerative findings without necrotic lesions, though the grade of perilobular cell infiltration rather increased than that in the biopsy specimen taken at the first operation. On the other side, parenchyma of the main liver showed atrophy with remark-

Tab. 6 Results of operation and liver regeneration (Cholangitic rabbits)

One-stage 80% Hepatectomized Group (5 rabbits)

Rabbit No.	Length of survival	Cause of death	Liver's per cent of body weight*
78	2 hours	Shock	— — —
79	4 days	Liver failure	— — —
80	more than 6 weeks	—	2.84 (58.2g/2.05kg)
84	more than 6 weeks	—	3.12 (61.8g/1.95kg)
85	2 days	Liver failure	— — —

* At autopsy 6 weeks after operation

Two-stage 80% Hepatectomized Group (6 rabbits)

Rabbit No.	Length of survival	Cause of death	Liver's per cent of body weight**
75	more than 6 weeks	—	3.31 (74.5g/2.25kg)
76	6 hours***	Hemorrhage	— — —
77	more than 6 weeks	—	3.27 (67.0g/2.05kg)
81	more than 6 weeks	—	2.94 (61.7g/2.10kg)
82	more than 6 weeks	—	3.14 (61.2g/1.95kg)
83	more than 6 weeks	—	2.83 (50.8g/2.15kg)

** At autopsy 6 weeks after first operation

*** Time after second operation

PLATE 5 CHOLANGITIC RABBITS

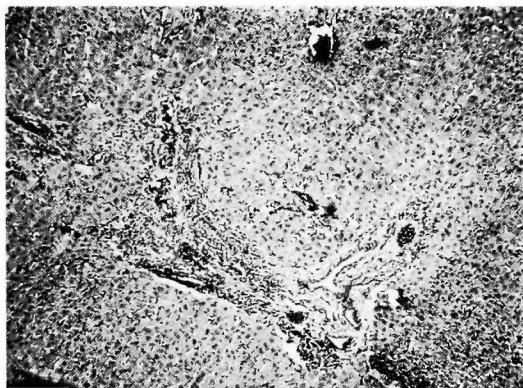


Fig. 30 Preoperative featur of the cholangitic liver (Rabbit 72). H-E $\times 100$

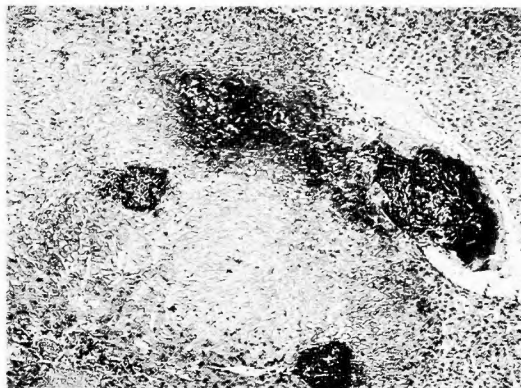


Fig. 31 One-stage hepatectomized rabbit's remaining lobe mass at death 4 days after the operation (Rabbit 79). H-E $\times 100$



Fig. 32 Hypertrophied lobe mass 3 weeks after the ligation of the portal branch (Rabbit 72). H-E $\times 100$



Fig. 33 Atrophied main liver 3 weeks after the ligation of the portal branch (Rabbit 72). H-E $\times 100$



Fig. 34 Two-stage hepatectomized rabbit's remaining lobe mass 6 weeks after the first operation (Rabbit 75). H-E $\times 100$

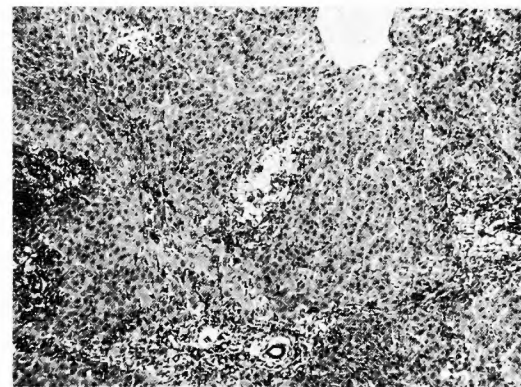


Fig. 35 One-stage hepatectomized rabbit's remaining lobe mass 6 weeks after the resection (Rabbit 84). H-E $\times 100$

able cellular infiltration in the proliferated connective tissue. In 2 cases out of 4 cholangitic rabbits, the weight of the lobe mass was less than 50% of the total liver weight 3 weeks after the operation. The occluded lobes of these cases adhered firmly to the splanchic organs (Fig. 32, 33, Tab. 2).

(b) Second operation

Six rabbits underwent the resection of the atrophied main liver 3 weeks after the first operation. During the resection, considerable bleeding was experienced in 2 cases with firm perihepatic adhesion. One case died of secondary hemorrhage.

In 5 successful cases, postoperative depression of the liver function was mild in general. They recovered to almost normal in 2 to 3 weeks (Fig. 19).

The weight of the remaining lobe mass reached to the extent of 2.83 to 3.31% of the body weight 3 weeks after the second operation i. e. 6 weeks after the first operation, indicating that remaining lobe mass restored to the original total hepatic weight. Microscopically, the lobules enlarged significantly and cellular infiltration was scarcely observed (Tab. 6, Fig. 34).

DISCUSSION

The studies of PONFICK¹⁹⁾, FISHBACK²⁰⁾ and HIGGINS & ANDERSON²¹⁾ revealed that almost complete regeneration of the liver took place in a short period, even when large segments were removed. The physiologic disturbances following extensive hepatectomy, being covered up by such great regenerative ability, have been apt to be taken as transitory and mild.

It has been, however, demonstrated that not a little influence is exerted on the organism when the liver which plays various important physiologic functions is extensively removed, with the advancement in the pathophysiologic studies on the liver resection.

For instance, MIKAMI²²⁾ reported that extensive hepatectomy, even in normal liver, led to hepatic and systemic circulatory disturbances, severe parenchymal damages and a depression of tissue respiration in the remaining liver, and subsequent hepatic failure in the early postoperative stage.

ATERMAN²³⁾ observed the appearance of watery vacuolation in the livers of rats as early as five minutes after partial hepatectomy, and pointed out that such vacuolation was identical with that observed in the liver in anoxic states.

On the other hand, SOEJIMA and his associates²⁴⁾ attached great importance to the effects of liver resection upon the portal circulation. They stated that the resection of more than 80% region of the liver caused a sudden disorder in the portal circulation, and finally the death of the animal in a very similar condition as seen in the complete interruption of the portal blood flow. They regarded the permissible limit of hepatectomy as 70% region of the total liver even in normal circumstances.

These disturbances would be much greater in clinical cases when the liver accompanied by more or less functional disturbances and parenchymal damages is to be resected extensively.

MIKAMI²⁵⁾ examined the relation between the preoperative liver function and the prognosis of the liver resection; out of 8 cases which showed more than 15% bromsulfa-

lein retention at 45 minutes, 6 cases died within one month after the operation, 4 cases out of 5 which showed less than 20% excretion rate in the hippuric acid test were poor in prognosis. He experienced the occurrence of postoperative hepatic insufficiency even in the cases whose hepatic failure were improved by powerful liver-protection therapy²⁰.

In the one-stage 80% hepatectomized rabbits, the control group in the present experiments, remarkable rise of the portal pressures appeared immediately after the operation and portalogram revealed portal circulatory disturbances. The decrease in the circulating blood volume was seen corresponding to the fall in the blood pressures. Severe parenchymal damages such as congestion, degenerative changes in liver cells, fat infiltration with decreasing glycogen were observed in the the remaining liver postoperatively. In this stage, significant depression of the liver function was determined in the laboratory studies.

In the experimentally damaged liver, the disturbances were all the more severe. The 80% resection of the cirrhotic liver led to the circulatory insufficiency and myocardial hypoxia, and the majority of the cirrhotic rabbits died of shock in early postoperative stage. The appearance of massive necrosis with infection was observed in the remaining liver of the cholangitic rabbits after the operation.

In clinical cases, an intensive care such as blood transfusion, oxygen-supply, administration of antibiotics and liver-protection therapy is of course taken for the prevention of the complications. The operation often results in poor prognosis, despite the full utilization of such treatments, when extensive hepatectomy is performed in the patients whose liver function has been impaired.

With the intention of performing the extensive resection for diseased liver safely, a method of liver resection performed in two stages was devised. Concerning this method, the following facts were proved. The ligation of the portal branches to the 80 % region of the liver exerted only a mild influence upon the portal and systemic circulation, and the unligated region did not show such parenchymal damages as seen in the remaining liver after the one-stage hepatectomy and started to regenerate actively.

DEWEESE and LEWIS²⁷ performed permanent ligation of portal branches to 70% region of the canine liver simultaneously with temporary occlusion of the hepatic artery to obtain a relatively bloodless approach to the liver. Such a procedure did not cause any significant physiologic disturbances in dogs studied as long as 6 months postoperatively.

In the case of the one-stage extensive hepatectomy, the excessive surgical attack on the liver not only causes sudden and extensive functional deficiency, but also produces circulatory disturbances and parenchymal damages in the remaining liver. Consequently the liver function is greatly impaired. Under these unfavorable conditions, liver regeneration is urged to take place.

At the time of the operation, if any infection has already existed in the liver, proliferation of the bacteria enables to cause irreversible damages of the remaining liver tissue. In addition, it is a widely accepted fact that liver failure is of great significance being related to the occurrence of the postoperative shock. There would be a risk of releasing hepatic vasodepressor materials which is one of the important factors in irreversible shock, into blood without being inactivated in anoxic liver²³.

On the contrary, when the ligation of the portal branches which does not give any

direct invasion on the liver is performed, parenchymal damages are estimated to be nothing. Unoccluded segments of the liver, therefore, can perform the function of the entire liver, exerting their functional reserve capacity sufficiently. Regeneration is provoked in the segments by an increase of the portal inflow which is regarded as intensive stimulus to liver regeneration.

Ligation of the portal branches to the 80% region of the cirrhotic liver could be performed without causing such physiological disturbances as might be deemed to endanger the animal's lives. Atrophy of the occluded segments and hypertrophy of the remaining segments of the liver were observed, though the proceeding of both atrophy and hypertrophy in this case is slower than in the case of a normal liver.

GOTO²⁹⁾ carried out ligation of the portal branches to the 63% area of the rat liver with carbon tetrachloride cirrhosis in an attempt to treat cirrhosis, and demonstrated that in the majority of the rats the hypertrophy of the remaining lobe was caused by proliferation of regenerated hepatic cells, and that the cirrhotic features prior to the operation were significantly improved with decrease of the connective tissue.

Ligation of the portal branches could be done safely in the cholangitic rabbits. The ligated segments, however, came to show strong inflammatory changes as well as atrophy with a tendency to adhere with the surrounding organs. Occurrence of such adhesion not only makes it difficult to perform the resection of the segments in the second operation, but also does not cause atrophy and hypertrophy of the liver, if a collateral circulation is formed between the occluded segments and the splanchnic organs. Consequently it can be hardly expected to increase the functional capacity of the unoperated side of the liver.

Accordingly it is highly required, in the performance of the two-stage hepatectomy, to take great care so as to produce the adhesion; for instance, to avoid damage on the surface of the liver during the first operation.

The disturbances in the hepatic circulation and function after removing the atrophied segments were quite mild. It seems to be due to the fact that the hypertrophy of the unoperated side of the liver caused to increase its functional capacity, and to extend its vascular bed at the time of the second operation. Thus, the two-stage hepatectomy succeeded in removing the 80% region of the cirrhotic liver.

The phenomenon that ligation of the portal branches leads to an atrophy of their controlling segments of the liver, and to a compensatory hypertrophy of the other segments, has been observed on the cat³⁰⁾ and the dog²⁷⁾ as well as on the rabbit³¹⁾ in literature. Such atrophy and hypertrophy observed under these circumstances are a phenomenon occurring commonly in a variety of animal species. It seems to be applicable to the human being. According to EHRHARDT³⁰⁾, NAUWERCK saw a case in which the left lobe of the liver was diminished to the size of a fist, with compensatory hypertrophy of the right lobe, as a result of long standing occlusion of the left portal branch. The rate of atrophy and hypertrophy due to the segmental occlusion of the portal inflow in the human liver is uncertain, but there is feasibility of clinical employment of the two-stage extensive hepatectomy.

In the human liver, the intrahepatic circulatory separation plane between the right and left portal branch lies on the gallbladder-cave line (CANTLIE)^{1~2)}. Two-stage hepatec-

tomy, therefore, can not be employed for the total right hepatic lobectomy whose dissection line lies along the ligamentum falciforme hepatis, but for right or left hemi-hepatectomy in which the dissection line corresponds to CANTLIE's line³²⁾.

At present, liver resection has been considered to be limited to the extent of total left lobectomy in the cases complicated with moderate to severe liver failure or hepatic cirrhosis, but this method would extend the limit of the resection as far as hemi-hepatectomy.

In addition, in the case of cancer of abdominal organs with hepatic metastasis in which performance of the resection of primary tumors combined with extensive hepatectomy is regarded as dangerous, it is advisable to remove the primary tumors and to ligate the portal branch to the metastatic side of the liver in the first place, and then to resect a half of the liver including the metastatic tumor secondly after the lapse of a certain period, during which the functional increase of the unoperated side can be expected³³⁾.

When a malignant tumor of the liver is to be treated with two-stage hepatectomy, it is feared that the tumor might enlarge or be metastasized during the interval of time from the ligation of the portal branch till the practice of resection of the tumor. Concerning this problem, HIRONO³⁴⁾, one of our co-workers, transplanted Ascitic Hepatoma 66F onto the rat liver to observe the condition of the tumor after the segmental interruption of the portal blood supply to the tumor implanted lobe, and demonstrated elongation of the surviving period and regression of the tumor in one-fourth of the cases. KRAUS and BERTRAN³⁵⁾ made a similar experiment on the rat liver on which Walker Carcinoma 256 had been transplanted, and reported that the regression was seen in 31.2% of the cases.

From these results of the experiments, it might be possible to expect that the growth of hepatic tumors is more or less inhibited by depriving the regional portal blood also in the human liver.

SUMMARY AND CONCLUSION

With an attempt to establish a safe extensive hepatectomy for a diseased liver, a method performed in two stages was devised, as summarized in the following ;

First operation : The portal branches to the hepatic segments destined to be resected are occluded. This procedure leads to a progressive atrophy of the parenchyma in the segments to be resected, and hypertrophy of the unoperated side of the hepatic tissue with increase in its functional capacity.

Second operation : The resection of the atrophied segments deprived of portal blood is performed after the lapse of certain period.

The 80% hepatectomy was performed according to this method in normal rabbits, experimentally cirrhotic and cholangitic rabbits. The obtained results were compared with those obtained by one-stage 80% hepatectomy.

(1) One-stage 80% hepatectomized group (Control group)

The resection of the 80% region of the liver in one stage led to portal and systemic circulatory disturbances, severe damages of the remaining hepatic tissue and remarkable depression of liver function. The majority of the cirrhotic rabbits died of shock in early postoperative stage. The appearance of massive necrosis with infection was observed in

the remaining hepatic tissue of the cholangitic rabbit. A number of the cases died of hepatic insufficiency, even in the normal rabbits.

(2) Two-stage 80% hepatectomized group

(a) First operation

The ligation of the portal branches to the 80% region of the liver exerted only a mild influence upon the portal and systemic circulation. Such a procedure did not cause serious physiologic disturbances in the cirrhotic and the cholangitic rabbits. Slight depression of the liver function was determined postoperatively, but it recovered in a short period with a tendency to improve the conditions compared with that prior to the segmental occlusion of the portal branches.

The unoccluded segments of the liver did not show such parenchymal damages as seen in the remaining liver after the one-stage hepatectomy and started to regenerate actively. The hypertrophy of the unoccluded segments was caused, even in the cirrhotic rabbits, by proliferation of regenerated liver cells and the cirrhotic features found prior to the first operation were significantly improved.

(b) Second operation

The hepatic segments deprived of portal blood were resected 3 to 4 weeks after the first operation. The operation was facile technically because the resected segments had atrophied to less than a half in volume, excluding some cases of the cholangitic rabbits with perihepatic adhesion.

Changes in portal and arterial pressures during operation, and postoperative depression of liver function were mild.

The remaining liver continued to hyperrophy, and restored almost to the original total hepatic weight in 2 to 3 weeks after the second operation.

It was proved that the two-stage extensive hepatectomy enabled us to remove the 80% region of the liver with comparative safety, even in the cirrhotic and cholangitic rabbit.

(Part of these data were presented before the 61st and 62nd Annual Meeting of Japanese Surgical Society.)

I would like to express my deepest gratitude to Prof. Dr. Ichio Honjo for his guidance and encouragement throughout this investigation.

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(* Written in Japanese)

和 文 抄 録

二 期 的 肝 広 汎 切 除 法

金沢大学医学部第二外科学教室（主任：本庄一夫教授）

小 坂 進

肝手術の最大の障壁であつた出血制御の問題が、肝内脈管機構に関する研究の進展によつて技術的に解決され、肝広汎切除が可能となつて、多くの肝疾患なかんずく肝癌の治療に期待がよせられているが、肝硬変症その他の肝障害が共存している症例では、術後致命的な肝不全に陥る危険性が高く、十分な肝切除を実施し得ない場合が少なくない。

かかる病的肝に対して安全に広汎切除を実施するには、何らかの手段によつて、その減退せる reserve capacity を増大せしめることが必要であるとの見解のもとに、門脈枝を結紮すると、肝の門脈血遮断領域が萎縮し、非遮断領域が肥大再生を営む現象を肝広汎切除に応用して、次の如く要約される術式を考案した。

第1回手術：肝の切除予定領域に流入する門脈枝を結紮遮断する。

第2回手術：残存肝に当る門脈血非遮断領域が再生肥大し、その functional capacity が増大するのをまつて、一定期間後に門脈血が遮断され萎縮している予定領域の切除を実施する。

本術式による肝広汎切除を、正常家兎、四塩化炭素肝硬変家兎および異種胆嚢で感作した後に腸内菌を感染せしめて作成した胆管炎家兎を対象として実施し、1期的切除の場合と、その生体に及ぼす影響を比較検討した。

(1) 1 期的80%肝切除群（対照群）

門脈および全身循環に著明な障害をきたし、術後残

存肝に激甚な組織障害があらわれ、その時期には肝機能も著しい低下を示した。肝硬変家兎の大多数は shock に陥り術後早期に死亡し、胆管炎家兎では残存肝組織に感染を伴つた広汎な壊死の発現がみられた。正常家兎でも多数が術後肝不全によつて死亡した。

(2) 2 期的80%肝切除群

肝の80%領域に流入する門脈枝結紮遮断の門脈および全身循環に及ぼす影響は比較的軽微で、肝硬変家兎および胆管炎家兎に対しても危険視される随伴障害をみることなく実施し得た。術後軽度の低下を示した肝機能も短期間で回復し、さらに術前より改善される傾向がみられた。肝の門脈血非遮断領域は、対照群の残存肝にみられたような組織障害に陥ることなく旺盛な再生肥大を営み、硬変肝においても肝再生が誘起され、硬化性変化もかなりの改善が認められた。

第1回手術より3～4週後に門脈血遮断領域の切除を実施したが、その領域が萎縮縮小しているため、切除操作自体も技術的に容易であつた。門脈および全身循環状態の変動ならびに術後の肝機能低下は軽微で、残存肝はさらに再生肥大を続けて、第2回手術後3週前後で、ほぼ術前全肝重量に達した。

本術式により硬変肝および胆管炎肝に対しても、肝広汎切除を比較的安全に実施し得ることが実験的に判明し、臨牀的に応用して肝切除手術適応の拡大が期待される。